

## **II. RESPONSE TO OFFICE ACTION**

### **A. Status of the Claims**

Claims 1-3, 9-10, 12-20, 21-29, 75-77, 83-106, 161, 162, 183, and 184 were pending in the case at the time of the Office Action, with claims 4-8, 11, 30-74, 78-82, 107-160, 163, 166, 168, and 171-175 having been withdrawn from consideration. Claims 2, 10, 11, 13, 15, 17, 18, 19, 20, 21, 22, 29, 30, 32, 76-86, 88, 90-100, 107, and 109 have been amended in the Amendment set forth herein. Claims 2, 32, 76, and 109 have been amended to correct the spelling of “chloropropyl.” Exemplary support for this spelling can be found on page 11, line 5 of the specification. Claims 2, 32, 76, and 109 have been amended to reflect that the moiety “methoxy(methoxy-dimethyl, pyridinyl)methyl-(sulfonyl)” refers to two separate moieties, methoxy and (methoxy-dimethyl pyridinyl)methyl-(sulfonyl). The methoxy moiety is one of the choices for the R<sup>3</sup> group. Exemplary support for these amendment can be found in the structure of omeprazole in claims 5, 35, and 79. The comma in “methoxy(methoxy-dimethyl, pyridinyl)methyl-(sulfonyl)” is a typographical error, and has been omitted in the Amendment set forth herein. Claim 22 has been amended to be in independent form. Claims 2, 9-11, 13, 15, 17-21, and 29-30 have been amended to depend from claim 22. Claim 100 has been amended to be an independent claim, and to pertain to any tumor suppressor gene. Claims 76-86, 88, 90-99, and 107 have been amended to depend from claim 100. Claims 1, 9, 12, 64, 75, 161-162, 164-165, 167, 169-170, and 176-184 have been canceled without prejudice or disclaimer. No new claims have been added.

### **B. The Maintained Anticipation Rejection of Claims 75-76, 83-97 and 99-100 Under 35 U.S.C. §102(e) by Camden I Are Overcome**

The Action maintains rejections of claims 75-77, 83-106, and 161-162 under 35 U.S.C. §102(e) as anticipated by Camden (U.S. Patent No. 6,262,093, hereinafter “Camden I”).

Applicants point out that in view of the Amendment set forth herein, claims 76-77 and 83-106 are at issue in this rejection.

The Examiner has agreed that the Applicants conceived of treating cancer cells with benzimidazoles prior to the filing date of Camden I, stating “The Declaration filed on 08/22/2005 under CFR 1.131 is sufficient to overcome the Camden et al reference [Camden I] ....as specifically drawn to a method of inducing apoptosis in cells expressing a tumor suppressor gene comprising administering an effective amount of benzimidazole to said cell, wherein the expression of the tumor suppressor gene by the cell and the benzimidazole results in the apoptosis of the cell.” Action, page 2. However, the Examiner contends that this declaration is insufficient with respect to *in vivo* methods. Applicants respectfully traverse, and respond as follows.

**1. Camden is not Prior Art Because Applicants Have Demonstrated Reduction to Practice of the Claimed Invention Before the Priority Date of Camden I**

Camden I is not prior art because the inventors reduced to practice the claimed invention prior to March 9, 1999, the priority date of Camden. In response to the previous Office Action, Applicants submitted a second declaration of inventors under 37 C.F.R. §1.131 (“Second Declaration,” attached as Appendix A) to show reduction to practice of the claimed invention prior to March 9, 1999.

The Second Declaration demonstrates reduction to practice of the claimed invention prior to March 9, 1999, the priority date of Camden I. In accordance with the requirement of 37 C.F.R. § 1.131(b), Applicants have provided in the Second Declaration a showing of facts of such character and weight as to establish reduction to practice prior to March 9, 1999.

Submitted as evidence of reduction to practice are two Exhibits (Exhibit 1 and Exhibit 2 of Second Declaration) setting forth experiments and results conducted prior to March 9, 1999.

Exhibit 2 of the Second Declaration sets forth findings that treatment of *p53* wild type lung cancer cells with fenbendazole inhibits growth. Second Declaration, paragraph 6 and Exhibit 2. The study evaluated growth of lung cancer cells or normal lung epithelium (NHBE) after treatment with fenbendazole (labeled FEN in Exhibit 2) and other agents. Both H1299 and H322 are *p53* deficient NSCLC cells and show modest growth inhibition by fenbendazole after 5-7 days of treatment. Second Declaration, paragraph 6 and Exhibit 2. In contrast, the *p53* wild-type cells A549 and H460 show dramatic inhibition of cell growth by fenbendazole that is evident by day 1-3 and 50-80% growth inhibition by day 5-7 of treatment. Second Declaration, paragraph 6 and Exhibit 2. The control normal cells, NHBE do not show growth inhibition by fenbendazole. Declaration, paragraph 6 and Exhibit 2. The results of this study were generated prior to March 9, 1999, the priority date of Camden.

Exhibit 1 of the Second Declaration sets forth results of experiments demonstrating reduction to practice of the claimed invention before the priority date of Camden I. Reduction to practice is evidenced by a copy of a FACS assay setting forth results of a cell cycle analysis involving A549 (*p53* wild type) non-small cell lung cancer (NSCLC) cells treated with fenbendazole (A549 7EN) or untreated control cells (A549C). Declaration, paragraph 3, 5 and Exhibit 1. The A549C cells show a standard profile of G1/S/G2 cells, indicating a dominant G1 population. Declaration, paragraph 5 and Exhibit 1. The fenbendazole treated cells show a depression of both G2 and S-phases and a G1 block. Declaration, paragraph 5 and Exhibit 1. Furthermore, the fenbendazole treated cells show a distinct sub-G0-G1 population indicative of apoptotic cells. Second Declaration, paragraph 5 and Exhibit 1.

The claims at issue in this rejection are directed to methods of treating a patient having cancer. Reduction to practice is shown by the fact that the cell types used in the experiments

conducted by the inventors (*i.e.*, human lung cancer cell lines A549, H1299, H322 cells, and H460) were human cells. Thus, it is submitted that the present Applicants carried out in the United States studies that demonstrate the reduction to practice of the claimed invention prior to the March 9, 1999, the priority date of Camden.

**2. Applicants, at the Very Least, Show as Much as Camden I**

The Examiner cites Freshney *et al.* (1983) and Dermer (1994) as allegedly teaching the unpredictability of extrapolating *in vitro* data to *in vivo* data. Applicants point out that these two references do not exemplify the state of the art in cancer therapeutics as of 2001. In a rapidly advancing field such as cancer therapeutics, references from 5-10 years prior to 2001 do not exemplify the state of the art in 2001. *In vitro* studies at the time of the priority date were commonplace in evaluating potential cancer therapeutic agents, and *in vitro* studies involving human cells would clearly reflect that studies involving patients are contemplated. Why else, after all, would one choose to study the effect of these agents on human cells?

Moreover, even if the more recent Dermer editorial reference was relevant, which the Applicants contest, the reference appears to distrust use of all cancer cell lines.

Why don't we have a cancer cure by now? The answer, in my opinion, is basic and essentially simple: The cell lines in which cancer is usually studied are unsuitable for the job. They do not mimic conditions in the human body. Dermer, page 320.

Thus, the Dermer reference would suggest that any data involving cancer cell lines is unsuitable. The Examiner's citation of Dermer, if relevant at all, would seem to apply to Camden I, because the only cancers to which benzimidazoles appear to have been administered in Camden I were cancer cell lines. See Camden I, column 14, lines 53-54, "*In vivo* Studies of Carbendazim on Cancer Cell Lines."

Applicants point out that in accordance with *In Re Stempel*:

A reference is valid only for what it discloses. If an applicant establishes priority with respect to that disclosure, and there is no statutory bar, the reference is of no effect at all... When a reference is not a statutory bar, Rule 131 (27 C.F.R. § 1.131) provides a procedure by which the applicant is permitted to show, if he can, that his date of invention was earlier than the date of the reference. The rule must be construed in accordance the rights given to inventors by statute and this excludes a construction permitting the further use of a reference as a ground of rejection after all pertinent subject matter in it has been antedated to the satisfaction of the Patent Office.

*In re Stempel*, 241 F.2d 755, 113 U.S.P.Q. 77, 81 (C.C.P.A. 1957)

Thus, because Applicants' pre-March 9, 1999 studies and the Camden I studies pertained to cell lines, in accordance with *In re Stempel*, Applicants have overcome Camden I as prior art.

**3. Camden I is Not Prior Art Because Applicants Conceived of Their Invention Before the Priority Date of Camden, and Were Diligent to the Time of the Priority Date of the Instant Application**

The Examiner, by maintaining the rejection, appears to question whether Applicants reduced their invention to practice as it pertains to *in vivo* methods. Applicants point out that even if reduction to practice prior to March 9, 1999 were questioned, Applicants have nevertheless overcome Camden I as prior art because they, at the very least, have established conception prior to March 9, 1999, with diligence to the time of the priority date of the instant application.

Conception, as discussed above, the discussion of which is incorporated into this section, is shown by the fact that experiments were conducted by the inventors prior to March 9, 1999, to assess the effect of benzimidazoles on growth inhibition of human cancer cell lines. The inventors, by conducting studies using human cancer cell lines and demonstrating induction of apoptosis by benzimidazoles, at the very least demonstrated conception of the invention as it pertains to *in vivo* methods. Why else, after all, would they have chosen to use human cancer cell lines? *In vitro* experiments using human cancer cell lines are commonly used as initial measures to evaluate the effect of anticancer agents. Further, the Examiner appears to have not

questioned Applicants' conception of the invention set forth in the claims in the Action. Thus, for the reasons set forth above, Applicants have demonstrated conception prior to March 9, 1999.

Further, Applicants were diligent from conception until the time of the priority date of the instant application. Applicants herein submit a third declaration under 37 C.F.R. § 1.131 (Appendix B) to show diligence in the reduction to practice of *in vivo* aspects of the claimed invention. In accordance with the requirement of 37 C.F.R. § 1.131(b), Applicants have provided in their declaration a showing of facts of such character and weight as to show conception prior to March 9, 1999, with diligence to the time of the priority date of the instant application. Because one of the inventors resides in India, Applicants require some additional time to submit a fully executed version of the Declaration to the U.S.P.T.O., and will do so in a supplemental response as soon as a fully executed version of the Declaration is obtained.

Diligence is established by the studies that resulted in a manuscript entitled "Potent Induction of Apoptosis by Anthelmintics in Human Lung Cancer Cells: Involvement of Wild-Type p53 and p21 Kinase Inhibitor." Third Declaration, paragraph 4, and Exhibit 1 of Appendix B. This manuscript is discussed at length in the Declaration submitted with the response to the Office Action dated June 28, 2004. The studies that are set forth in this manuscript, and the preparation of this manuscript, were conducted before January 14, 2000. Third Declaration, paragraph 4.

Additionally, diligence is shown in laboratory notes describing a series of experiments pertaining to the administration of a benzimidazole drug for the treatment of cancer. Third Declaration, paragraph 5, and Exhibit 2 of Appendix B. These notes evaluated, for example: 1) dosage response for the induction of apoptosis through the administration of a benzimidazole to A549 lung cancer cells; 2) VEGF expression after administration of a benzimidazole to A549

cells; 3) western blots of cancer cells after the administration of a benzimidazole; 4) growth inhibition after administration of a benzimidazole; and 5) inhibition of tumor growth *in vivo* after administration of a benzimidazole. *Id.* These experiments took place between November 10, 2000 and September 9, 2001. *Id.*

Concurrent with these experiments, diligence is also established in the preparation of a manuscript of the results of studies, including studies conducted using animal models, entitled “Mebendazole: A Novel Microtubule Agent Having Potent Antitumor Activity,” which was submitted for publication on October 25, 2001. Third Declaration, paragraph 6, and Exhibit 3. In accordance with the findings set forth in the *in vitro* data, the *in vivo* data summarized in this manuscript establishes that mebendazole inhibits lung cancer growth in an animal model. Third Declaration, paragraph 8, and Exhibit 3 of Appendix B.

Thus, the Third Declaration of Inventors establishes that Applicants were diligent from the conception of the present invention prior to March 9, 1999, the priority date of Camden I, up to the time of the priority date of the instant application, which was January 11, 2001. Thus, Camden I has been overcome by Applicants as prior art.

#### **4. Conclusion**

In view of the above, Applicants respectfully assert that Camden I has been overcome as prior art. Therefore, Applicants respectfully request that the rejections of claims 75-77, 83-106, 161-162 and 184 under 35 U.S.C. §102(e) over Camden I be withdrawn.

**C. The Maintained Rejections Under 35 U.S.C. §103(a) Are Overcome**

**1. Claims 75-76, 83-97 and 99-106 Are Not Obvious Over Camden I in Combination with Perdomo, *et al.***

Claims 75-76, 83-97 and 99-106 are rejected as obvious under 35 U.S.C. §103(a) over Camden I in combination with Perdomo, *et al.* Applicants traverse.

As described above, the discussion of which is herein incorporated into this section, Camden I is not available as prior art.

Because Camden I is not available as a prior art reference, the rejection of claims 75-76, 83-97 and 99-100 under 35 U.S.C. § 103(a) based on Camden I and Perdomo *et al.* cannot be sustained. Therefore, Applicants respectfully request the rejection of these claims be withdrawn.

**2. Claims 75-77, 83-97, 99, 161-162 and 184 Are Not Obvious Over Camden I in Combination with Delatour *et al.***

Claims 75-77, 83-97, 99, 161-162 and 184 are rejected as obvious under 35 U.S.C. §103(a) over Camden I in combination with Delatour, *et al.* Applicants traverse.

As described above, the discussion of which is herein incorporated into this section, Camden I is not available as prior art.

Furthermore, Delatour does not teach or suggest the missing limitations that are not disclosed in Camden I. Delatour includes no information pertaining to induction of apoptosis as a result of administration of a benzimidazole and expression of a tumor suppressor gene. Nor does Delatour include any information pertaining to inhibition of cancer as a result of expression of a tumor suppressor and administration of a benzimidazole. As a result, the Examiner has not met his burden of establishing a *prima facie* case of obviousness. Therefore, Applicants respectfully request the rejection of these claims be withdrawn.

**E. The Rejection Under 35 U.S.C. §112, Second Paragraph, Is Overcome**

Claim 9 is rejected under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention. Specifically, the Examiner states that the phrase, “the dose of benzimidazole is at least 0.05 mg/mL” renders the claim indefinite. Applicants traverse.

Applicants have canceled claim 9 in the Amendment set forth herein. Therefore, this rejection is moot.

**F. The Rejections Under 35 U.S.C. §112, First Paragraph, Are Overcome**

Claims 161-162 and 183-184 are rejected under 35 U.S.C. §112, first paragraph, as failing to comply with the written description requirement. The Examiner states that the proviso limitation of these claims, which sets forth that if R<sup>3</sup> is a H or chloro, then R<sup>2</sup> cannot be H if R<sup>1</sup> is carbamate, is not sufficiently set forth in the specification so as to convey to one of ordinary skill in the art that the Applicants contemplated the inclusion of the benzimidazole derivatives having this limitation. Applicants traverse.

Applicants point out that each of the claims at issue in this rejection have been canceled without prejudice or disclaimer. By canceling these claims, Applicants in no way concede that these claims failed to comply with the written description requirement.

In view of the above, Applicants respectfully request withdrawal of the written description rejections under 35 U.S.C. §112, first paragraph.

**G. The Rejections of Claims 1-2, 12, 15-19, 21, 29, 75-76, 83, 85 and 88-96 Under 35 U.S.C. §102(b) by Camden II Are Overcome**

Claims 1-2, 12, 15-19, 21, 29, 75-76, 83, 85 and 88-96 have been rejected by the Examiner under 35 U.S.C. §102(b) as anticipated by Camden (U.S. Patent No. 5,880,144, hereinafter “Camden II”). Specifically, the Examiner states that Camden II teaches: a method of

killing lung, breast and colon tumor cells comprising administering a benzimidazole derivative; a method of treating a patient having cancer comprising administering an effective amount of a benzimidazole derivative to inhibit the growth of the cancer; and methods of oral or parenteral administration, intravenous injection, or injection into or around the tumor. The Examiner further states that although Camden II does not specifically teach that the administration of benzimidazole induces apoptosis, such a limitation would be an inherent property based on Camden I. Finally, the Examiner states that while Camden II does not explicitly characterize the tumor cell lines as expressing a tumor suppressor gene such as p53, such a limitation would be an inherent property based on Applicant's specification. Applicants traverse.

Applicants point out that that in the Amendment set forth herein, claim 22, which was not rejected and thus not considered anticipated by Camden II, has been amended to be in independent form. Claims 2, 15, 17-19, 21, and 29 have been amended to depend from claim 22. Further, claim 100, which includes the limitation of "determining the tumor suppressor gene status of the cancer cell," has been amended to be in independent form. The Examiner appears to have considered this limitation nonobvious. Claims 76, 83, 85, and 88-96 have been amended such that these claims all depend from claim 100. The remaining claims at issue in this rejection have been canceled without prejudice or disclaimer. Thus, in view of the above, this rejection is moot.

#### **H. The New Rejections Under 35 U.S.C. §103(a) Are Overcome**

##### **1. The Rejection of Claims 3, 77, 161-162, and 182-183 As Being Unpatentable Over Camden II in Combination with Delatour *et al.* or Nasr *et al.* are Overcome**

Claims 3, 77, 161-162 and 182-183 have been rejected under 35 U.S.C. §103(a) as being unpatentable over Camden II in combination with Delatour *et al.* or Nasr *et al.* Camden II is discussed above. Delatour *et al.* is said to teach embryotoxic and antimitotic properties of

benzimidazole compounds, the a method of inhibiting tumor growth in mice comprising administering the benzimidazole derivative, mebendazole. Nasr *et al.* is said to teach *in vivo* anticancer activity of certain carbamates against intraperitoneally implanted murin lymphocytic leukemia and lymphoid lymphoma. It is asserted in the Action that it would have been *prima facie* obvious to one of ordinary skill in the art to combine reference teachings to inhibit tumor growth because each of the benzimidazoles disclosed in the references have structural similarities and utilities. Applicants respectfully traverse.

Applicants point out that in view of the Amendment set forth herein, claim 3 now depends from claim 2, which in turn depends from claim 22. Claim 22 was not at issue in this rejection. Further, claim 77 has been amended to depend from claim 100, which was not at issue in this rejection. The remaining claims at issue in this rejection have been canceled without prejudice or disclaimer. Therefore, this rejection is moot.

**2. The Rejection of Claims 23-28 and 101-106 as Being Unpatentable Over Camden II in Combination with Delatour *et al.* or Nasr *et al.* in view of Perdoma *et al.* are Overcome**

Claims 23-28 and 101-106 have been rejected under 35 U.S.C. §103(a) as being unpatentable over Camden II in combination with Delatour *et al.* or Nasr *et al.* Camden II is discussed above in view of Perdoma *et al.* Camden II, Delatour *et al.*, and Nasr *et al.* are discussed above. Perdoma *et al.* is said to teach determining p53 status by western blot analysis or other methods such as PCR, and using this determination to predict response to therapy in certain patients. According to the Action, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to determine the status of a tumor suppressor gene in a tumor cell prior at administering a benzimidazole derivate using techniques such as Western blot and PCT or other methods of analysis. Applicants respectfully traverse.

Claims 23-28 each depend from claim 22, which was not involved in this rejection. Claim 22 has been amended to be an independent claim. Similarly, claims 101-106 each depend from independent claim 100, which was not involved in this rejection. Therefore, this rejection is moot.

**3. The Rejection of Claims 13-14 and 86-87 as Being Unpatentable Over Camden II in Combination with Delatour *et al.* or Nasr *et al.* in View of Lucci *et al.* are Overcome**

Claims 13-14 and 86-87 have been rejected under 35 U.S.C. §103(a) as being unpatentable over Camden II in combination with Delatour *et al.* or Nasr *et al.* Camden II is discussed above in view of Lucci *et al.* Camden II, Delatour *et al.*, and Nasr *et al.* are discussed above. Lucci *et al.* is said to teach multidrug resistance modulators and doxorubicin synergize to elevate ceramide levels and elicit apoptosis in drug-resistant cancer cells, specifically drug resistant human breast cancer cell lines. Thus, the Action states that it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to use a multidrug resistant cell line, such as a breast cancer cell, in the method taught by Camden II in view of the teachings of Lucci *et al.* Applicants respectfully traverse.

Claims 13 has been amended to depend from claim 22, which, as discussed above, has been amended to be an independent claim. Claim 14 depends from claim 13. Claim 86 has been amended to depend from claim 100, which was considered to be nonobvious in view of the cited references. Further, claim 87 depends from claim 86. Therefore, this rejection is moot.

**4. Conclusion**

In view of the above, the Examiner has failed to establish a *prima facie* case of obviousness. Therefore, it is respectfully requested that the new rejections under 35 U.S.C. §103(a) should be withdrawn.

## **I. Conclusion**

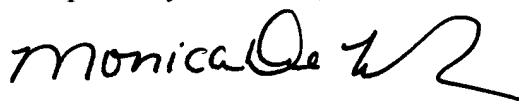
Applicants believe that the present document is a full and complete response to the Office Action dated November 16, 2005. In conclusion, Applicants submit that, in light of the foregoing remarks, the present case is in condition for allowance, and such favorable action is respectfully requested.

### **III. PETITION FOR EXTENSION OF TIME**

Pursuant to 37 C.F.R. § 1.136(a), Applicants petition for an extension of time of two months to and including April 17, 2006 (in view of the Saturday, Sunday, Holiday rule), in which to respond to the Office Action dated November 16, 2005. Pursuant to 37 C.F.R. § 1.17, a check in the appropriate amount for a two-month extension of time is included. If the check is inadvertently omitted, or should any additional fees under 37 C.F.R. §§ 1.16 to 1.21 be required for any reason relating to the enclosed materials, or should an overpayment be included herein, the Commissioner is authorized to deduct or credit said fees from or to Fulbright & Jaworski Deposit Account No. 50-1212/INRP:095US.

The Examiner is invited to contact the undersigned attorney at (512) 536-5639 with any questions, comments or suggestions relating to the referenced patent application.

Respectfully submitted,



Monica A. De La Paz  
Reg. No. 54,662  
Attorney for Applicants

FULBRIGHT & JAWORSKI L.L.P.  
600 Congress Avenue, Suite 2400  
Austin, Texas 78701  
512.474.5201 (telephone)  
512.536.4598 (fax)

Date: April 17, 2006